Global harmonization in outbreak research: this time, it's working

The ISARIC clinical characterisation group

To make clinical and biological observations in a time-frame likely to benefit patients during disease outbreaks, coordination in global research must match the speed of spread of novel pathogens. Time is short. Circumstances compel us to work together, across the world, to understand, treat, and prevent COVID-19.

During previous outbreaks, clinical research has often been set up *ad hoc* and conducted in silos, using different methodologies and designs. This limits opportunities to compare results, or to combine smaller studies to get answers quickly. It is perhaps self-evident that harmonisation of clinical investigation during outbreaks is desirable. The WHO clinical management research prioritization group identified harmonized clinical characterization research as its first priority for COVID-19.

Harmonisation creates opportunities for individual investigators to compare results or collaborate, without applying burdens or obligations. Also, at least for the authors of this article, the quality and breadth of research is improved by collaborative development and peer review of shared protocols. For example, in the current outbreak, a clinician might design a study to identify risk factors for progression, co-infections, and mechanisms of critical illness. Fewer clinicians would consider the need to obtain serum for groups with the capability to make new assays for seroepidemiology, or peripheral blood mononuclear cells for monoclonal antibody therapeutics. Wide collaboration leads to better, faster science.

Achieving global coordination is difficult enough at the best of times; during a crisis it may seem impossible. But in each new crisis, the same questions arise again and again. So the same designs can tackle them. We believe that global harmonisation is possible, at least in the intermittently-indispensable field of outbreak research. To achieve it we need to make harmonized investigation *easier* than establishing isolated independent studies, respect autonomy and sovereignty of investigators, and relinquish normal routes of academic recognition for this work.

To this end, in 2012 a single, standardized generic research protocol was created for clinical characterization of any emerging infection (the ISARIC/WHO Clinical Characterisation Protocol, CCP: isaric.net/ccp). This took years of international and cross-speciality consensus-building.[1] Since the fundamental research questions in a new outbreak are predictable, the protocol can be established and approved in "peacetime", maintained in a hibernating state, then rapidly implemented when required. Carefully-designed, flexible biological sampling schedules are included in tiers according to local resources, modular additional studies for specific situations, and scalable case report forms.[1] These tools were released under an open-source licence: anyone can download these materials and

use, adapt or distribute them. Clinical research feels like it is 95% about filling in forms. We filled in some of the forms, so you don't have to.

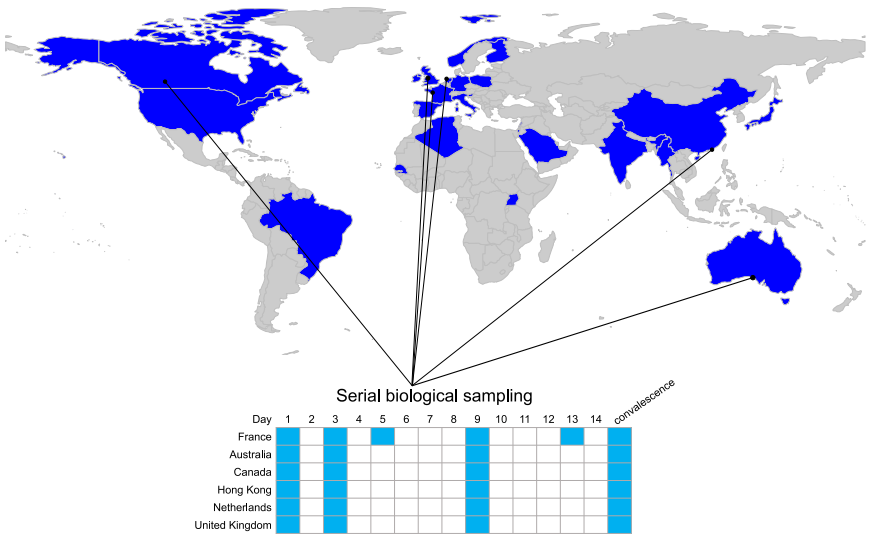

Figure 1: Sample schedules in use in selected countries

The CCP was implemented in Brazil in response to the emergence of Zika virus and chikungunya virus in Latin America, facilitating studies of viral shedding and serology.[2] It was used for cohort studies of critically-ill patients with MERS.[3] The Uganda Virus Research Institute is using it to study severe acute febrile illness and severe influenza.[4]

The value of this approach is becoming apparent in the age of COVID-19. The original reports on clinical findings in COVID-19 utilised harmonised data collection.[5,6] 46 countries have registered to record clinical data using the ISARIC CCP CRF and investigators in many countries are planning to use the CCP biological sampling protocol to conduct coordinated studies of transmission, prognostication, pathogenesis and diagnostics.

Understanding the genetic mechanisms underlying susceptibility[7] may directly advance our understanding of disease mechanisms[8] and possible treatments,[9] but robust studies require very large numbers of critically ill patients. This requires open, collegiate, global collaboration. GenOMICC (Genetics Of Mortality In Critical Care, https://genomicc.org) is an open consortium in which clinicians have been recruiting critically ill patients since 2016. Importantly, this work is led by the clinicians treating the patients, in collaboration with experts in host genetics.

Operating clinical trials at global scale presents many additional challenges, but even in this domain, significant progess has been made. In advance this catastrophe, the critical care community created a highly-efficient randomised, embedded multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP, https://www.remapcap.org). This is a single trial, established in 13 countries, with the capacity to test new hypotheses quickly. Perhaps most ambitious of all, WHO has developed a global platform - the SOLIDARITY trial - for evaluation of widely-available interventions to treat COVID-19.

Catastrophes bring about surges in innovation and drastic social change. Within our own community, we believe that perceptions of academic excellence have long under-valued teamwork and collegiality. We hope our colleagues across the world will make use of these tools, either in collaboration or independently, to harmonise clinical research efforts and fulfil the duties of medical science to humanity in the shortest possible time.

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